REMARKS

I. Status of the claims

Claims 1-12 and 17-36 are pending. The Examiner withdrew claims 29 and 30 for allegedly "being drawn to a distinct invention from the one being examined (due to a lack of unity of the invention)." Office Action at page 2.

Claims 1-7, 9, 12, and 24 have been amended. Claims 8, 10, 11, and 19 have been cancelled. Claims 13-16 were previously cancelled. All of the amendments are supported by the originally-filed specification and claims. Applicants have amended claims 1, 8, and 24 to recite that the parathyroid hormone formulation is in stable liquid form, and to specify certain components of the claimed formulation. These elements are supported, for instance, by original claim 10, Examples 1, 2, 3, 4, and 6, and Tables II and IV.

II. The presently claimed liquid parathyroid hormone formulation is distinct from the prior art formulations of parathyroid hormone

The presently claimed invention produces a highly concentrated liquid formulation of parathyroid hormone ("PTH") that can be stored for prolonged periods of time as a liquid with minimal, if any, loss of protein stability. Applicants underscore herein several key differences between the presently claimed human parathyroid hormone liquid formulation and the lyophilized PTH formulations described in the cited prior art.

(i) ***The present invention uses sodium chloride in liquid preparations of parathyroid hormone, which the prior art does not presage***

Contrary to conventional wisdom, Applicants' claimed liquid PTH formulation comprises sodium chloride. The liquid formulation stabilizes the PTH protein for a prolonged period of time, *i.e.*, at least two weeks. See, for instance, Example 6 at page 11 and Table IV, which show that PTH in liquid was stable after two weeks of refrigerated and room temperature storage conditions. The formulation techniques of the prior art, however, do not describe sodium chloride in ***liquid*** formulations of high concentrations of PTH which are stable over a prolonged period of time. Rather, the only prior art use of sodium chloride with PTH describes using PTH in much smaller amounts in a unit dose ***lyophilized*** form, which is then reconstituted for a single use.

One reason for avoidance of sodium chloride in prior-art liquid PTH was the understanding that chloride ions induced dimerization of PTH protein in liquid. This aspect of the conventional wisdom on liquid PTH formulations is evidenced, for example, in CA 2,234,724 (of record) and the entry 8051-x ("Parathyroid Hormone"), at page 1338, of the MARTINDALE: THE EXTRA PHARMACOPEIA, The Pharmaceutical Press, London, 29th Edition, 1989. The latter reference, which is appended to this paper, states explicitly that "sodium chloride solutions" of parathyroid hormone "**should not be used** as they often cause precipitation" (emphasis added). Contrary to the Examiner's assertion, therefore, the relevant literature, which CA 2,234,724 and THE EXTRA PHARMACOPEIA illustrate, actually taught away from incorporating sodium chloride in a liquid PTH formulation.

In contravention of the conventional wisdom, Applicants' investigations into the effect of ionic strength on PTH stability (see present Example 3) revealed that liquid aliquots of PTH formulation "were not affected by increased ionic strength in terms of PTH stability" (specification, page 9, lines 24-25). Thus, Figure 3 shows

that the stability of PTH after nine months of storage, with various concentrations of sodium chloride at +4°C, was essentially the same as the stability of PTH measured immediately at "0" months, the beginning of the experiment

Applicants also discovered that the stability of PTH in an illustrative liquid formulation (0.5 mg/ml PTH, 2 mg/ml NaCl, and 50 mg/ml mannitol) at pH 5.5 was 100% after one month and 99% after six months of storage at +4°C (see entry "2G" in Table II). Indeed, the degradation rate calculated for this liquid formulation of PTH was only 0.19% per month, contrary to what the skilled artisan would have expected.

(ii) ***Unlike prior-art formulations, a PTH formulation as claimed uses a high concentration of PTH in solution***

It also was understood by the skilled artisan that aggregation and precipitation of protein from solution was more likely to occur with high concentrations of protein, such as those presently recited. Applicants discovered, however, that "the stability of PTH is markedly increased, when the PTH concentration is increased" for liquid formulations (page 8, lines 21-24). See Applicants' Example 1, Figure 1, and Table II. Unexpectedly, therefore, it was found that "stability is superior at PTH concentrations above 0.3 mg/ml" for liquid formulations (*id.*). Thus, Applicants report that preferred concentrations of PTH for use in the presently claimed formulations can be "0.3 – 5 mg/ml or 0.3 – 3 mg/ml; or above 1 mg/ml, such as 1 – 10 mg/ml, 1 – 5 mg/ml; 1 – 3 mg/ml; or 1 – 2 mg/ml" (specification at page 5, lines 16-18).

(iii) ***A PTH formulation as claimed can be stored in liquid form for at least two weeks***

Before the present invention, a stable liquid preparation, capable of being administered as a multidose unit over a period of time, was not known in the prior art. Prior-art PTH preparations were formulated in single-dose amounts, eliminating the need to store any remaining liquid dose, and the corresponding

need to determine whether the liquid PTH remained stable for any length of time. Based on such experience, the skilled artisan could not have predicted, and had no basis for predicting, how long reconstituted PTH would remain stable in liquid.

Applicants, on the other hand, determined that pharmaceutical formulations of the present invention had very low and, therefore, desirable degradation rates, as well as high levels of purity that spanned periods of 2 weeks to 24 weeks (*i.e.*, 6 months) and beyond. See the Examples and Tables II and VI.

III. Summary of the Office Action

(i) Claims 8 and 9 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,496,801 ("Holthuis") and U.S. Patent No. 5,563,122 ("Endo").

(ii) Claims 1-7, 10-12, 17-18, 21-23, 26-28, and 31-36 are rejected under 35 U.S.C. § 103(a) as unpatentable over Holthuis in view of Endo.

(iii) Claims 19, 20, 24, and 25, are rejected under 35 U.S.C. § 103(a) as unpatentable over Holthuis and Endo further in view of U.S. Patent No. 5,547.939 ("Selsted").

Applicants respectfully disagree with the Examiner's rationale for rejecting the claims and traverse each of the rejections for the reasons that follow below.

IV. Claims 8 and 9 are not obvious

The Examiner has maintained the rejection of claims 8 and 9 as unpatentable over the combination of U.S. Patent No. 5,496,801 ("Holthuis") and U.S. Patent No. 5,563,122 ("Endo"). Since Applicants have cancelled claim 8, this rejection applies only to claim 9. Claim 9 defines concentrations of parathyroid hormone, NaCl, mannitol, and citrate buffer in a stable, liquid pharmaceutical formulation of PTH.

According to the Examiner, "it would have been obvious for one of skill in the art at the time of the invention, to modify the preparation of Holthuis, by adding a sodium chloride solution as taught by Endo, because Endo teaches that a combination of sodium chloride and sugar achieves a higher stability for a PTH preparation." Office Action of September 10, 2002, page 6. However, the prior art explicitly taught away from adding sodium chloride to PTH liquids. Hence, the Applicants' invention can not be considered obvious when the only known prior art discussing liquid formulations of PTH and sodium chloride state that such a combination will not result in a stable liquid formulation.

(a) *Applicants surprisingly discovered that sodium chloride could be formulated into a highly concentrated liquid formulation of PTH without any undesirable dimerization and precipitation of PTH.*

It would *not* have been obvious for the skilled artisan to add sodium chloride to a liquid solution of PTH because the prior art, as illustrated by CA 2,234,724 (supra) and MARTINDALE: THE EXTRA PHARMACOPEIA (supra), taught that PTH dimerizes and precipitates in solutions containing sodium chloride. It was Applicants discovery that sodium chloride could be formulated into a highly concentrated liquid formulation of PTH *without* any undesirable dimerization and precipitation.

(b) ***Endo et al. teaches that sodium chloride can cause shrinkage of a lyophilized PTH cake and reduces PTH stability, neither of which is of issue in the presently claimed invention, which claims a stable liquid PTH formulation.***

Holthuis *et al.* and Endo *et al.* teach the stabilization of *lyophilized* PTH powders. See, column 3, lines 26 – 31 of Holthuis *et al.* All of the examples in Endo *et al.* describe a "lyophilized preparation" of PTH. Indeed, Endo states that "[A]n object of the present invention is to provide a *lyophilized preparation of PTH,*" (emphasis added, column 1, lines 38-39). But Endo also relates that an undesirable effect of sodium chloride is that "when the amount of sodium chloride exceeds 20% of the weight of sugar, a lyophilized cake of the preparation will suffer shrinkage and the stability tends to decrease," (emphasis added, column 2, lines 15-17). Thus, the skilled artisan, after reading Endo, would seek to control the sodium chloride-to-sugar ratio to avoid such "shrinkage" and decreased stability.

By contrast, the presently claimed *liquid* formulation suffers no such detriment. Indeed, the ratio of sodium chloride-to-mannitol recited in claim 9 is as high as 25% (5 mg/ml sodium chloride to 20 mg/ml mannitol). There is no guidance in Endo *et al.* on the effect of sodium chloride on liquid formulations. Instead, the skilled artisan would understand from the teachings of MARTINDALE: THE EXTRA PHARMACOPEIA (supra) and CA 2,234,724 (supra) that sodium chloride precipitates PTH from a liquid preparation and should be avoided.

(c) ***Endo et al. uses a PTH concentration that is 1000-fold lower than is presently claimed and, therefore, is much more unlikely to precipitate upon addition of sodium chloride.***

The skilled artisan would understand that chloride ion-induced precipitation of protein is more likely to occur when sodium chloride is added to a highly concentrated protein solution. In keeping with this understanding, Endo *et al.* adds sodium chloride to a very low concentration, 1 μg-150 μg, of

lyophilized PTH (column 2, lines 36-38), whereas the presently claimed invention requires 0.3 mg/ml (300 μg) to 10 mg/ml (10000 μg) of liquid PTH. Thus, the PTH concentration of the present invention is up to 1000 times greater than the concentration of PTH described in Endo *et al.* The skilled artisan would not be motivated to raise the concentration of PTH described in Endo *et al.* or Holthuis *et al.* to that presently recited and also incorporate sodium chloride. Furthermore, the skilled artisan would be informed by conventional wisdom that highly concentrated proteins can precipitate, which is not a desirable property for an injectable PTH liquid.

Accordingly, claim 9 is not rendered obvious by the cited prior art, and Applicants respectfully request that the Examiner withdraw this rejection.

V. Claims 1-7, 10-12, 17-18, 21-23, 26-28, and 31-36 are not obvious

The Examiner rejected claims 1-7, 10-12, 17-18, 21-23, 26-28, and 31-36, as unpatentable over Holthuis *et al.* (supra) in view of Endo *et al.* (supra) because, "it would have been obvious to one having ordinary skill in the art at the time the invention was made to include sodium chloride in the formulation of Holthuis *et al.* with a reasonable expectation of success. One would have been motivated to do so because Endo *et al.* demonstrate that addition of sodium chloride in addition to mannitol, further stabilizes PTH." Office Action at pages 5 and 6.

As Applicants have detailed above, neither Holthuis *et al.* nor Endo *et al.* teach the addition of sodium chloride to a liquid formulation of PTH. Accordingly, the claims are free from objection, and Applicants respectfully request that the Examiner withdraw this rejection.

VI. Claims 19, 20, 24, and 25 are not obvious

The Examiner rejected claims 19, 20, 24, and 25 as unpatentable over Holthuis *et al.* (supra) in view of Endo *et al.* (supra), further in view of Selsted (U.S. Patent No. 5,547,939). According to the Examiner, Selsted teaches "methods of inhibiting survival or growth of a microorganism using a composition comprising EDTA, which disrupts microbial membranes" (page 6 of the Office Action). Thus, "it would have been obvious to one having ordinary skill in the art at the time of the invention was made to further include a preservative, e.g. EDTA, in the formulations taught by Holthuis *et al.* in combination with Endo *et al.*" Office Action at page 6.

However, Selsted's "composition" is actually a tryptophan-rich, *indolicidin protein analog* that exhibits "broad spectrum antimicrobial activity" (column 2, lines 35-40). Thus, the primary antimicrobial agent of Selsted is an indolicidin analog protein of a specific amino acid sequence, and *not* a chemical as prescribed by the present claims.

According to Selsted, "other compounds or compositions can also be administered *in conjunction with* indolicidin peptides to further increase their antimicrobial properties," so long as such compounds do not inhibit the activity of indolicidin (emphasis added; column 7, lines 13-15). Thus, Selsted speaks to the *combination* of the antimicrobial indolicidin analog and, for instance, EDTA, which "disrupts microbial membranes."

Selsted teaches that "a pharmaceutical composition comprising an indolicidin analog can be administered to a subject by various routes," column 7, lines 22-23. Selsted does not teach or suggest formulating a drug with only EDTA and no indolicidin. Indeed, none of Selsted's examples reflect experiments conducted with EDTA and, in fact, EDTA appears only once and in passing at column 7, line18 of the patent.

The skilled artisan will find in Selsted absolutely no guidance in selecting appropriate concentrations, amounts, or doses of EDTA for formulation of a non-indolicidin-containing drug composition. Furthermore, Selsted says nothing on how EDTA affects the stability of an active ingredient in a pharmaceutical composition, and more particularly, it does not provide any guidance as to how to formulate it with PTH. Accordingly, the skilled artisan, having read Selsted, would not know how much, or whether it would even be feasible, to add EDTA to the PTH formulation of either of Holthuis *et al.* or Endo *et al.*

By contrast, Applicants have demonstrated the direct antimicrobial effects of m-cresol, benzoyl alcohol, and EDTA on highly concentrated PTH liquid formulations. See Example 6, page 11, and Tables IV and VII at pages 16 and 17. For example, Applicants showed that the stability of PTH under refrigerated and room temperature conditions, in the presence of m-cresol, EDTA, and benzoyl alcohol, was almost 100% after two-weeks storage.

Thus, Applicants concluded that "these preservatives gave a satisfactory protection against microbial growth after challenge," and that "PTH is stable in the presence of efficient preservatives, thus allowing for the use of the formulation in a multidose product," page 12, lines 1-5.

Selsted does not remedy the deficiencies of either Holthuis *et al.* or Endo *et al.* Moreover, as outlined above, neither Holthuis nor Endo teach or suggest the incorporation of sodium chloride in highly concentrated liquid formulations of PTH. Thus, Applicants respectfully request that the Examiner withdraw this rejection.

VIII. Conclusion

Accordingly, Applicants request that the amendments presented herewith be entered, the accompanying arguments be considered and the claims be allowed to pass to issue. The Examiner is invited to contact the undersigned by telephone if it is thought that a phone interview would expedite an early allowance.

Respectfully submitted,

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